II. REMARKS

Preliminary Remarks:

Current Status of the claims

Claims 2, 30, and 33 are amended, claims 23-27 are canceled, and new claims 39-42 are added by the present amendment. Upon entry of the amendment, claims 2, 3, 5, 16-21, 30, and 32-42 will be pending in the application.

Claim 2 is amended by deleting step (c), which describes assaying to select antibodies that compete for binding to gp39 with murine antibody 24-31, by deleting references in steps (e) and (f) to antibodies that compete for binding to gp39 with murine antibody 24-31, and by re-labeling the steps of the claimed method consecutively as steps (a)-(e).

Claims 30 and 33 are amended to refer to step (c) of claim 2, in accord with the amendment of claim 2 discussed above.

New claims 39-42 are directed to the disclosed method for providing anti-human gp39 antibodies that inhibit the interaction of human gp39 with CD40 and are non-agonistic of an activation response by human $CD4^+$ T-cells, which method comprises (a) obtaining monoclonal anti-human gp39 antibodies that inhibit the interaction of human gp39 with CD40, and (b) assaying *in vitro* to identify soluble anti-human gp39 antibodies of step (a) that are non-agonistic of an activation response by purified human $CD4^+$ T-cells that have been cultured *in vitro* with immobilized anti-CD3 antibodies, the activation response selected from the group consisting of T-cell proliferation, the production of interleukin-2 (IL-2), the production of interleukin-4 (IL-4), and the production of interferon γ (IFN- γ).

Support for the amendment of claims 2, 30, and 33, and for new claims 39-42 is found in the specification, *e.g.*, on page 23, lines 1-8, and on page 37, lines 7-29.

The applicant does not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserves the right to pursue such subject matter in continuing applications.

Patentability Remarks:

35 U.S.C. §103(a)

Claims 2, 3, 5, 16-21, 23-27, 30, and 33-39 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable in view of Black *et al.* (U.S. Patent No. 6,001,358), in combination with Schrader *et al.* (U.S. Patent No. 5,627,052), Burkly *et al.* (US2002/0028202 A1), and Wilson *et al.* (U.S. Patent No. 6,372,208 B1), and further in view of Van den Eertwegh *et al.* (1993) and Roy *et al.* (1993), for the reasons of record.

The applicants submit that the claimed invention would not have been obvious to one of ordinary skill in the art at the time the invention was made in view of the combined teachings of the cited references, because the combination of cited references would not have taught or suggested all of the elements of the claimed invention. Furthermore, neither the combination of cited references nor the general knowledge at the time the invention was made would have provided one of ordinary skill in the art with suggestion or motivation to perform the claimed methods, nor would they have provided one of ordinary skill in the art with a reasonable expectation that the claimed methods could be performed successfully.

To establish a *prima facie* case of obviousness, the examiner must show that the prior art references themselves or the knowledge generally available to one of ordinary skill in the art would (1) provide some suggestion or motivation to modify or combine reference teachings to obtain the claimed invention, (2) teach or suggest all of the claim limitations, and (3) provide a reasonable expectation that the claimed invention can be made or used successfully. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicants' disclosure. *See* In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), *also* In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) citing In re Raynes, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992), *and* M.P.E.P. § 2142.

A. The cited references failed to teach or suggest all elements of the claimed invention

Independent claims 2 and 39 both specify a method comprising the steps of (i) obtaining monoclonal anti-human gp39 antibodies that inhibit the interaction of human gp39 with CD40, and (ii) assaying *in vitro* to identify soluble anti-human gp39 antibodies of the previous step that are non-agonistic of an activation response by purified human $CD4^+$ T-cells that have been

cultured *in vitro* with immobilized anti-CD3 antibodies, wherein the activation response is selected from the group consisting of T-cell proliferation, the production of interleukin-2 (IL-2), the production of interleukin-4 (IL-4), and the production of interferon γ (IFN- γ).

The present invention is based on the applicants' discovery of an efficient *in vitro* assay for identifying soluble anti-human gp39 antibodies that are non-agonistic of an activation response by purified human $CD4^+$ T-cells that have been cultured *in vitro* with immobilized anti-CD3 antibodies, the activation response being selected from the group consisting of T-cell proliferation, the production of IL-2, the production of IL-4, and the production of IFN- γ.

As discussed in the previous response, the combination of the cited references would not have taught or suggested the claimed methods comprising a step of assaying *in vitro* to identify soluble anti-human gp39 antibodies of the previous step that are non-agonistic of an activation response by purified human $CD4^+$ T-cells that have been cultured *in vitro* with immobilized anti-CD3 antibodies, the activation response being selected from the group consisting of T-cell proliferation, the production of IL-2, the production of IL-4, and the production of IFN- γ.

Black *et al.* (U.S. Patent No. 6,001,358), the primary reference, discloses anti-human gp39 antibodies that compete for binding to human gp39 with murine antibody 24-31, and therapeutic methods in which such anti-gp39 antibodies are administered to treat multiple sclerosis and other diseases. Black *et al.* does not teach or suggest assaying to identify soluble anti-human gp39 antibodies that inhibit the interaction of human gp39 with CD40 and are non-agonistic of an activation response by purified human $CD4^+$ T-cells that have been cultured *in vitro* with immobilized anti-CD3 antibodies, which activation response is selected from the group consisting of T-cell proliferation. Examples 2, 3, 12 and 15 of Black *et al.* describe *in vitro* and *in vivo* studies of the effect of anti-gp39 antibodies on B cell proliferation and differentiation (Ig production), and Examples 11, 13, 14, 16, and 17 describe biochemical assays of the ability of the disclosed anti-gp39 antibodies to bind to gp39 and block binding to CD40. The cited examples of Black *et al.*, like the document as a whole, are concerned with the effects on B cells of signals delivered by $gp39^+$ T cells to the B cells via CD40.

The cited secondary references, considered in combination with Black *et al.*, also fail to teach or suggest the claimed invention comprising a step of assaying *in vitro* to identify soluble anti-human gp39 antibodies of the previous step that are non-agonistic of an activation response by purified human $CD4^+$ T-cells that have been cultured *in vitro* with immobilized anti-CD3 antibodies, the activation response being selected from the group consisting of T-cell proliferation, the production of IL-2, the production of IL-4, and the production of IFN- γ.

Schrader *et al.* (U.S. Patent No. 5,627,052) describes a general method for screening a population of antibody-producing B cells to identify an antibody that has a desired function, such as the ability to mimic an activity of a biologically active factor, *e.g.*, an interleukin, colony stimulating factor, or interferon (*e.g.*, *see* col. 8, lines 38-49). Schrader et al. clearly teaches that successful operation of the method described by Schrader et al. requires selection of a suitable "indicator system" comprising cells that respond to the antibody by altering the function of interest. For example, *see* col. 7, lines 24-34, and col. 8, lines 22-37.

Burkly *et al.* (US2002/0028202 A1) describes a general method of assaying or screening the ability of an antagonist such as an antibody to bind to a cellular cytokine receptor and block a response of a cell to a cytokine (*e.g.*, *see* pages 7-8 and 13). For example, Burkly *et al.* describes an assay in which an antibody that binds to a cytokine receptor on the surface of a T cell blocks cytokine-mediated stimulation of proliferation of activated T cells *in vitro* (*see* paragraph [0136] on page 13].

Wilson *et al.* (U.S. Patent No. 6,372,208 B1) teaches that antibodies that block the interaction of CD40 ligand on a T helper cell with CD40 antigen on a B cell prevents the activation of T helper cells *in vivo* (*e.g.*, *see* col. 6, line 61, to col. 7, line 7).

Van den Eertwegh *et al.* describe experiments that indicate that $gp39^+$ T cells produce IL-2, IL-4, and IFN-γ *in vivo* in the spleens of mice (*see* pages 1557 and 1560-61).

Roy *et al.* describe experiments that show that purified $CD4^+$ T cells that have been cultured in the presence of immobilized anti-CD3 antibody express gp39 (*see* pages 2501-4), and that IL-2, IL-4, and IFN-γ inhibit expression of gp39 by purified $CD4^+$ T cells that are cultured in the presence of immobilized anti-CD3 antibody (*see* page 2501).

None of the cited references teaches or suggests that the binding of a soluble anti-human gp39 antibody to gp39 antigen on purified human $CD4^+$ T-cells that have been cultured *in vitro* with immobilized anti-CD3 antibodies is capable of modulating (either stimulating or inhibiting) an activation response by said purified human $CD4^+$ T-cells selected from the group consisting of T-cell proliferation, the production of IL-2, the production of IL-4, and the production of IFN-γ. **Therefore, the combination of cited references neither teaches nor suggests the method of the claimed invention comprising assaying *in vitro* to identify soluble anti-human gp39 antibodies of the previous step that are non-agonistic of an activation response by purified human $CD4^+$ T-cells that have been cultured *in vitro* with immobilized anti-CD3 antibodies, wherein the activation response is selected from the group consisting of T-cell proliferation,**

the production of IL-2, the production of IL-4, and the production of IFN- γ. Since the cited combination of references do not teach or suggest all of the claim limitations, the examiner has not established a *prima facie* case of obviousness.

B. <u>The prior art taught away from performing the method of the claimed invention</u>

At the time the invention was made, the prior art taught away from the claimed invention and so would not have provided a suggestion or motivation to one of ordinary skill in the art to perform the method of the claimed invention comprising assaying *in vitro* to identify soluble anti-human gp39 antibodies of the previous step that are non-agonistic of an activation response by purified human $CD4^+$ T-cells that have been cultured *in vitro* with immobilized anti-CD3 antibodies, wherein the activation response is selected from the group consisting of T-cell proliferation, the production of IL-2, the production of IL-4, and the production of IFN- γ.

At the time the invention was made, the interaction of anti-human gp39 antibodies with T cells that results in the inhibition of T cell activation was considered by persons of skill in the art to require the involvement of an antigen-presenting cell (APC) that presents antigen to the T cell at the same time that an anti-gp39 antibody blocks the interaction between gp39 on the T cell surface and a gp39 ligand (*e.g.*, CD40) on the surface of the antigen-presenting cell. The view that inducing T cell tolerance by anti-human gp39 antibodies, either *in vivo* or *in vitro*, requires the interaction between a T cell and an APC such as a B cell, is clearly and expressly described in Noelle et al. (International Patent Application No. WO 1995/006666, which was cited in the IDS filed on May 9, 2002), as shown in the following text from the Summary of the Invention on page 2, line 29, to page 3, line 20:

> "The current invention is based, at least in part, on the discovery that cell-surface molecules which mediate contact-dependent helper effector functions also play a critical role in the response of T cells to antigens. In particular, it has been discovered that, under appropriate conditions, interference of an interaction between gp39 on a T cell and a ligand on a cell which is presenting antigen to the T cell can induce antigen-specific T cell tolerance. Accordingly, the cell which presents antigen to the T cell requires an interaction between a gp39 ligand (e.g., CD40) on the cell and gp39 on the T cell to be able to provide signals necessary for activation of the T cell. Inhibition of the interaction between the gp39 ligand and gp39 prevents T cell activation and rather induces antigen-specific T cell tolerance.

> The methods of the invention pertain to induction of antigen-specific T cell tolerance. The methods involve contacting a T cell with: 1) a cell which presents antigen to the T cell and has a ligand on the cell surface which interacts with a receptor on the surface of the T cell which mediates contact-dependent helper effector functions; and 2) an antagonist of the receptor on the surface of a T cell which mediates contact-dependent helper effector functions. The antagonist inhibits the interaction of the receptor with it's ligand. A T cell can be contacted with the cell which presents antigen and the antagonist in vitro, or alternatively, the cell and the antagonist can be administered to a subject to induce T cell tolerance in vivo.
>
> …The cell which presents antigen to a T cell is preferably a B cell. The B cell can be a small, resting B cell. To induce T cell tolerance to a soluble antigen, the B cell can be contacted with the antigen prior to contact with the T cell (e.g., prior to administration to a subject). In another embodiment, to induce T cell tolerance to alloantigens, the cell which is used to present antigen to the T cell is an allogeneic cell. The allogeneic cell can be, for example, an allogeneic B cell, allogeneic bone marrow, allogeneic spleen cells or allogeneic cells in peripheral blood."

Black et al. similarly teaches that T cell activation and T cell-mediated responses are inhibited by anti-gp39 antibodies *in vivo* because the anti-gp39 antibodies block CD40 signaling in B cells and dendritic cells and interfere with antigen presentation to T cells. For example, *see* col. 32, lines 10-14. None of the teachings of the cited secondary references refutes or contradicts the multicellular model for the inhibition of T cell activation and T cell-mediated responses by anti-gp39 antibodies described by Noelle et al. and Black et al. Accordingly, one of ordinary skill in the art at the time the invention was made would reasonably have understood that anti-gp39 antibodies inhibit T cell activation and T cell-mediated responses by blocking CD40 signaling of B cells or dendritic cells and interfering with antigen presentation to T cells. By expressly teaching that anti-gp39 antibodies inhibit T cell activation responses mediated by multicellular interactions involving APCs such as B cells and dendritic cells, Noelle et al. and Black et al. taught away from the claimed method, which comprises assaying to determine the ability of anti-gp39 antibodies to affect activation responses of purified human T cells *in vitro*. The prior art therefore would not have provided one of ordinary skill in the art at the time the invention was made with suggestion or motivation to modify or combine reference teachings to obtain the claimed invention comprising assaying *in vitro* to identify soluble anti-human gp39 antibodies of the previous step that are non-agonistic of an activation response by purified human $CD4^+$ T-

cells that have been cultured *in vitro* with immobilized anti-CD3 antibodies, wherein the activation response is selected from the group consisting of T-cell proliferation, the production of IL-2, the production of IL-4, and the production of IFN- γ. Since the primary reference and other prior art taught away from the claimed method, and the cited combination of prior art references failed to provide one of ordinary skill in the art with suggestion or motivation to combine the reference teachings to obtain the claimed invention, the examiner has not established a *prima facie* case of obviousness.

C. The cited combination of references also failed to provide a reasonable expectation that the method of the claimed invention could be performed successfully

At the time the invention was made, it was not known and could not have been predicted by one of ordinary skill in the art that soluble anti-human gp39 antibodies are capable of binding to gp39 of purified human $CD4^+$ T-cells that have been cultured *in vitro* in the presence of immobilized anti-CD3 antibodies and modulating T cell activation responses such as T cell proliferation and the production of the cytokines IL-2, IL-4, and IFN- γ. References such as Blair et al. and Blotta et al. had demonstrated that anti-human gp39 antibodies bound to a solid substrate such as a bead or the interior surface of a culture dish are agonistic of T cell activation responses by purified human $CD4^+$ T-cells cultured *in vitro* in the presence of immobilized anti-CD3, as discussed in previous responses. However, the prior art did not describe or suggest whether and how T cell activation responses of purified human $CD4^+$ T-cells that have been cultured *in vitro* in the presence of immobilized anti-CD3 antibodies are affected by soluble anti-human gp39 antibodies. **As neither the combination of cited references nor the general knowledge of one of ordinary skill in the art at the time the invention was made would have enabled one of ordinary skill in the art to predict that the method of the claimed invention could be performed with a reasonable expectation of success, a *prima facie* case of obviousness has not been established.**

In view of the foregoing, withdrawal of the rejection of the claims under 35 U.S.C. § 103(a) as allegedly having been obvious in view of Black *et al.*, Schrader *et al.*, Burkly *et al.*, and Wilson *et al.*, and further in view of Van den Eertwegh *et al.*, and Roy *et al.*, is respectfully requested.

III. CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

/ thomas a cawley jr /

Date: June 11, 2007

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